09/441140

1-176 (Cancelled).

177 (Previously Presented). The therapeutic composition of claim 210 or 211, wherein said genetically-engineered monoclonal antibody is a single-chain antibody.

178-209 (Cancelled).

210 (Currently Amended). A therapeutic composition, comprising:

a pharmaceutical formulation comprising

(1) a pharmaceutically acceptable carrier and

(2)(a) a genetically-engineered antibody that binds beta-amyloid and inhibits aggregation of beta-amyloid or maintains the solubility of soluble beta-amyloid to an extent at least as great as that obtainable with antibody AMY-33, or

(b) a fragment of the genetically-engineered antibody of (a) that binds beta-amyloid and inhibits aggregation of beta-amyloid or maintains the solubility of soluble beta-amyloid to an extent at least as great as that obtainable with antibody AMY-33,

wherein said genetically-engineered antibody is obtained by genetically engineering the DNA encoding a monoclonal antibody that

(i) binds beta-amyloid and inhibits aggregation of beta-amyloid or maintains the solubility of soluble beta-amyloid to an extent at least as great as that obtainable with antibody AMY-33, and

(ii) is obtainable using an immunogen consisting of a peptide consisting of residues 1-28 of beta-amyloid; and

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wherein said antibody or fragment is not conjugated with a detectable moiety.

211 (Currently Amended). The therapeutic composition of claim 210, wherein said genetically-engineered antibody of (2)(a) binds human beta-amyloid and inhibits aggregation of human beta-amyloid or maintains the solubility of soluble human beta-amyloid to an extent at least as great as that obtainable with antibody AMY-33, or said fragment of (2)(b) binds human beta-amyloid and inhibits aggregation of human beta-amyloid or maintains the solubility of soluble human beta-amyloid to an extent at least as great as that obtainable with antibody AMY-33, and said genetically-engineered antibody of (2)(a) is obtained by genetically engineering the DNA encoding a monoclonal antibody that binds human beta-amyloid and inhibits aggregation of human beta-amyloid or maintains the solubility of soluble human beta-amyloid to an extent at least as great as that obtainable with antibody AMY-33 and said monoclonal antibody is obtainable using an immunogen consisting of a peptide consisting of residues 1-28 of human beta-amyloid.

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212 (Currently Amended). A therapeutic composition, comprising:

a pharmaceutical formulation comprising

(1) a pharmaceutically acceptable carrier and

(2)(a) a human monoclonal antibody that binds beta-amyloid and inhibits aggregation of beta-amyloid or maintains the solubility of soluble beta-amyloid to an extent at least as great as that obtainable with antibody AMY-33, or

(b) a fragment of the human monoclonal antibody of (a) that binds beta-amyloid and inhibits aggregation of beta-amyloid or maintains the solubility of soluble beta-amyloid to an extent at least as great as that obtainable with antibody AMY-33,

wherein said human monoclonal antibody is obtainable using an immunogen consisting of a peptide consisting of residues 1-28 of beta-amyloid.

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213 (Currently amended). The therapeutic composition of claim 212, wherein said human monoclonal antibody of (2)(a) binds beta-amyloid and inhibits aggregation of human beta-amyloid or maintains the solubility of soluble human beta-amyloid to an extent at least as great as that obtainable with antibody AMY-33, or said fragment of (2)(b) binds beta-amyloid and inhibits aggregation of human beta-amyloid or maintains the solubility of soluble human beta-amyloid to an extent at least as great as that obtainable with antibody AMY-33, and wherein said human monoclonal antibody of (a) is obtainable using an immunogen consisting of a peptide consisting of residues 1-28 of human beta-amyloid.

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214 (Currently Amended). A method of making a therapeutic composition comprising (1) a pharmaceutically acceptable carrier and (2)(a) a genetically-engineered antibody that binds beta-amyloid and inhibits aggregation of beta-amyloid or maintains the solubility of soluble beta-amyloid to an extent at least as great as that obtainable with antibody AMY-33, or (b) a fragment of the genetically-engineered antibody of (a),

which fragment binds beta-amyloid and inhibits aggregation of beta-amyloid or maintains the solubility of soluble beta-amyloid to an extent at least as great as that obtainable with antibody AMY-33, said method comprising:

selecting a monoclonal antibody that

(i) binds beta-amyloid and inhibits aggregation of beta-amyloid or maintains the solubility of soluble beta-amyloid to an extent at least as great as that obtainable with antibody AMY-33, and

(ii) is obtainable using an immunogen consisting of a peptide consisting of residues 1-28 of beta-amyloid;

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genetically engineering the DNA encoding said selected monoclonal antibody so as to produce a genetically-engineered antibody that binds beta-amyloid and inhibits aggregation of beta-amyloid or maintains the solubility of soluble beta-amyloid to an extent at least as great as that obtainable with antibody AMY-33, or a fragment of a genetically engineered antibody, which fragment binds beta-amyloid and inhibits aggregation of beta-amyloid or maintains the solubility of soluble beta-amyloid to an extent at least as great as that obtainable with antibody AMY-33; and

formulating said genetically engineered monoclonal antibody or fragment with a pharmaceutical carrier into a pharmaceutical formulation that is a therapeutic composition.

215 (New). A therapeutic composition, comprising:

a pharmaceutical formulation comprising

(1) a pharmaceutically acceptable carrier and

(2)(a) a genetically-engineered antibody that binds beta-amyloid and inhibits aggregation of beta-amyloid or maintains the solubility of soluble beta-amyloid to an extent at least as great as that obtainable with antibody AMY-33, or

(b) a fragment of the genetically-engineered antibody of (a) that binds beta-amyloid and inhibits aggregation of beta-amyloid or maintains the solubility of soluble beta-amyloid to an extent at least as great as that obtainable with antibody AMY-33,

wherein said genetically-engineered antibody is obtained by genetically engineering the DNA encoding a monoclonal antibody that

(i) binds beta-amyloid and inhibits aggregation of beta-amyloid or maintains the solubility of soluble beta-amyloid to an extent at least as great as that obtainable with antibody AMY-33, and

(ii) recognizes an epitope within residues 1-28 of beta-amyloid, and

wherein said antibody or fragment is not conjugated with a detectable moiety.

216 (New). The therapeutic composition of claim 215, wherein said genetically-engineered antibody of (2)(a) binds beta-amyloid and inhibits aggregation of human beta-amyloid or maintains the solubility of soluble human beta-amyloid to an extent at least as great as that obtainable with antibody AMY-33, or said fragment of (2)(b) binds beta-amyloid and inhibits aggregation of human beta-amyloid or maintains the solubility of

soluble human beta-amyloid to an extent at least as great as that obtainable with antibody AMY-33, and said genetically-engineered antibody of (2)(a) is obtained by genetically engineering the DNA encoding a monoclonal antibody that binds beta-amyloid and inhibits aggregation of human beta-amyloid or maintains the solubility of soluble human beta-amyloid to an extent at least as great as that obtainable with antibody AMY-33 and said monoclonal antibody recognizes an epitope within residues 1-28 of human beta-amyloid.

217 (New). The therapeutic composition of claim 215 or 216, wherein said genetically-engineered monoclonal antibody is a single-chain antibody.

218 (New). A method of making a therapeutic composition comprising (1) a pharmaceutically acceptable carrier and (2)(a) a genetically-engineered antibody that binds beta-amyloid and inhibits aggregation of beta-amyloid or maintains the solubility of soluble beta-amyloid to an extent at least as great as that obtainable with antibody AMY-33, or (b) a fragment of the genetically-engineered antibody of (a), which fragment binds beta-amyloid and inhibits aggregation of beta-amyloid or maintains the solubility of soluble beta-amyloid to an extent at least as great as that obtainable with antibody AMY-33, said method comprising:

selecting a monoclonal antibody that

(i) binds beta-amyloid and inhibits aggregation of beta-amyloid or maintains the solubility of soluble beta-

amyloid to an extent at least as great as that obtainable with antibody AMY-33, and

(ii) recognizes an epitope within residues 1-28 of beta-amyloid;

genetically engineering the DNA encoding said selected monoclonal antibody so as to produce a genetically-engineered antibody that binds beta-amyloid and inhibits aggregation of beta-amyloid or maintains the solubility of soluble beta-amyloid to an extent at least as great as that obtainable with antibody AMY-33, or a fragment of a genetically engineered antibody, which fragment binds beta-amyloid and inhibits aggregation of beta-amyloid or maintains the solubility of soluble beta-amyloid to an extent at least as great as that obtainable with antibody AMY-33; and

formulating said genetically engineered monoclonal antibody or fragment with a pharmaceutical carrier into a pharmaceutical formulation that is a therapeutic composition.

219 (New). A therapeutic composition, comprising:

a pharmaceutical formulation comprising

(1) a pharmaceutically acceptable carrier and

(2)(a) a genetically-engineered antibody that binds beta-amyloid and disaggregates an aggregate of β-amyloid, or

(b) a fragment of the genetically-engineered antibody of (a) that binds beta-amyloid and disaggregates an aggregate of β-amyloid,

wherein said genetically-engineered antibody is obtained by genetically engineering the DNA encoding a monoclonal antibody that

(i) binds beta-amyloid and disaggregates an aggregate of β-amyloid and

(ii) is obtainable using an immunogen consisting of a peptide consisting of residues 1-28 of beta-amyloid, and

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wherein said antibody or fragment is not conjugated with a detectable moiety.

220 (New). The therapeutic composition of claim 219, wherein said genetically-engineered antibody of (2)(a) binds beta-amyloid and disaggregates an aggregate of human β-amyloid, or said fragment of (2)(b) binds beta-amyloid and disaggregates an aggregate of human β-amyloid, and said genetically-engineered antibody of (2)(a) is obtained by genetically engineering the DNA encoding a monoclonal antibody that binds beta-amyloid and disaggregates an aggregate of human β-amyloid and said monoclonal antibody is obtainable using an immunogen consisting of a peptide consisting of residues 1-28 of human beta-amyloid.

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221 (New). The therapeutic composition of claim 219 or 220, wherein said genetically-engineered monoclonal antibody is a single-chain antibody.

222 (New). A therapeutic composition, comprising:

a pharmaceutical formulation comprising

(1) a pharmaceutically acceptable carrier and

(2)(a) a human monoclonal antibody that binds beta-amyloid and disaggregates an aggregate of β-amyloid, or

(b) a fragment of the human monoclonal antibody of (a) that binds beta-amyloid and disaggregates an aggregate of β-amyloid,

wherein said human monoclonal antibody is obtainable using an immunogen consisting of a peptide consisting of residues 1-28 of beta-amyloid.

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223 (New). The therapeutic composition of claim 222, wherein said human monoclonal antibody of (2)(a) binds beta-amyloid and disaggregates an aggregate of human β-amyloid, or said fragment of (2)(b) binds beta-amyloid and disaggregates an aggregate of human β-amyloid, and wherein said human monoclonal antibody of (a) is obtainable using an immunogen consisting of a peptide consisting of residues 1-28 of human beta-amyloid.

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224 (New). A method of making a therapeutic composition comprising (1) a pharmaceutically acceptable carrier and (2)(a) a genetically-engineered antibody that binds beta-amyloid and disaggregates an aggregate of β-amyloid, or (b) a fragment of the genetically-engineered antibody of (a), which fragment binds beta-amyloid and disaggregates an aggregate of β-amyloid, said method comprising:

selecting a monoclonal antibody that

(i) binds beta-amyloid and disaggregates an aggregate of β-amyloid, and

(ii) is obtainable using an immunogen consisting of a peptide consisting of residues 1-28 of beta-amyloid;

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genetically engineering the DNA encoding said selected monoclonal antibody so as to produce a genetically-engineered

antibody that binds beta-amyloid and disaggregates an aggregate of β-amyloid, or a fragment of a genetically engineered antibody, which fragment binds beta-amyloid and disaggregates an aggregate of β-amyloid; and

formulating said genetically engineered monoclonal antibody or fragment with a pharmaceutical carrier into a pharmaceutical formulation that is a therapeutic composition.

225 (New). A therapeutic composition, comprising:

a pharmaceutical formulation comprising

(1) a pharmaceutically acceptable carrier and

(2)(a) a genetically-engineered antibody that binds beta-amyloid and disaggregates an aggregate of β-amyloid, or

(b) a fragment of the genetically-engineered antibody of (a) that binds beta-amyloid and disaggregates an aggregate of β-amyloid,

wherein said genetically-engineered antibody is obtained by genetically engineering the DNA encoding a monoclonal antibody that

(i) binds beta-amyloid and disaggregates an aggregate of β-amyloid and

(ii) recognizes an epitope within residues 1-28 of beta-amyloid, and

wherein said antibody or fragment is not conjugated with a detectable moiety.

226 (New). The therapeutic composition of claim 225, wherein said genetically-engineered antibody of (2)(a) binds beta-amyloid and disaggregates an aggregate of human β-amyloid,

or said fragment of (2)(b) binds beta-amyloid and disaggregates an aggregate of human β-amyloid, and said genetically-engineered antibody of (2)(a) is obtained by genetically engineering the DNA encoding a monoclonal antibody that binds beta-amyloid and disaggregates an aggregate of human β-amyloid and said monoclonal antibody recognizes an epitope within residues 1-28 of human beta-amyloid.

227 (New). The therapeutic composition of claim 225 or 226, wherein said genetically-engineered monoclonal antibody is a single-chain antibody.

228 (New). A method of making a therapeutic composition comprising (1) a pharmaceutically acceptable carrier and (2)(a) a genetically-engineered antibody that binds beta-amyloid and disaggregates an aggregate of β-amyloid, or (b) a fragment of the genetically-engineered antibody of (a), which fragment binds beta-amyloid and disaggregates an aggregate of β-amyloid, said method comprising:

selecting a monoclonal antibody that

(i) binds beta-amyloid and disaggregates an aggregate of β-amyloid, and

(ii) recognizes an epitope within residues 1-28 of beta-amyloid;

genetically engineering the DNA encoding said selected monoclonal antibody so as to produce a genetically-engineered antibody that binds beta-amyloid and disaggregates an aggregate of β-amyloid, or a fragment of a genetically engineered

antibody, which fragment binds beta-amyloid and disaggregates an aggregate of β-amyloid; and

formulating said genetically engineered monoclonal antibody or fragment with a pharmaceutical carrier into a pharmaceutical formulation that is a therapeutic composition.

Support for the fact that the antibody must bind to the beta-amyloid is found in the specification at -

Col. 3, ll. 45-47:

> These anti-aggregation molecules are able to bind to a native target molecule epitope with a high binding constant …

Col. 5, ll. 30-32:

> The antibodies … must bind to an epitope on the target molecule which is a region responsible for folding or aggregation.

Col. 6, ll. 7-14:

> A method of treating a protein aggregation disease intracellularly includes the steps of preparing (Haber. 1992; Harlow & Lane, 1988) or selecting an anti-aggregation molecule, such as a monoclonal antibody, genetically engineered monoclonal antibody fragment or peptide that mimics the binding site of an antibody, that binds to an aggregating protein which is the cause of a disease and which prevents aggregation and yet allows the protein to be bio-active.

Col. 6, ll. 21-26:

> In the preferred embodiment the human monoclonal antibody that binds to an aggregating protein and

which prevents aggregation is utilized. In a further preferred embodiment the monoclonal antibody is an anti-β-amyloid and is designated AMY-33 which recognizes amino acids 1-28 of β-amyloid.

Col. 16, ll. 5-6:

Binding of mAb AMY-33 to βA4 prevents self-aggregation of the β-amyloid, …

Support for the fact that the immunogen consists of a peptide consisting of residues 1-28 of human beta-amyloid may be found in the present specification at:

Col. 11, ll 33-37:

In general, monoclonal antibodies may be prepared against a synthetic peptide based on the sequence, or prepared recombinantly by cloning techniques or the natural gene product and/or portions thereof may be isolated and used as the immunogen. [Note it does not say "used as an immunogen"; it says "used as the immunogen." Thus the immunogen consists of this natural gene product or portion thereof.]

Col. 15, ll. 35-38:

… mAb AMY 33 (Stern et al., 1990), purchased from Zymed, San Francisco, Calif., USA, raised against peptides … 1-28 … of the β-amyloid. [Note that this establishes that peptides 1-28 of the β-amyloid is an example of the immunogen referred to in the previous quotation.]